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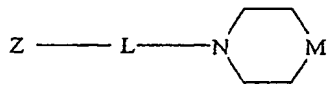


(I)

(57) Abstract

Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by structural formula (I), and physiologically acceptable salts thereof.

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# CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR

## RELATED APPLICATION

This application is a continuation-in-part of U.S. Serial No. 09/146,827, filed September 4, 1998, the entire teaching of which are incorporated herein by reference.

## BACKGROUND OF THE INVENTION

Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promote recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of effector cells in chronic inflammation. The chemokines characterized to date are related in primary structure. They share four conserved cysteines, which form disulfide

chemokines (α-chemokines), and the C-C chemokines (β-chemokines), in which the first two conserved cysteines are separated by an intervening residue, or adjacent respectively (Baggiolini, M. and Dahinden, C. A., *Immunology Today*, *15*:127-133 (1994)).

The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), eotaxin, and human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and activators of monocytes or lymphocytes but do not appear to be chemoattractants for neutrophils. Chemokines, such as RANTES and MIP-1α, have been implicated in a wide range of human acute and chronic inflammatory diseases including respiratory diseases, such as asthma and allergic disorders.

The chemokine receptors are members of a superfamily of G protein-coupled receptors (GPCR) which share structural features that reflect a common mechanism of action of signal transduction (Gerard, C. and Gerard, N.P., *Annu Rev. Immunol.*, *12*:775-808 (1994); Gerard, C. and Gerard, N. P., *Curr. Opin. Immunol.*, *6*:140-145 (1994)). Conserved features include seven hydrophobic domains spanning the plasma membrane, which are connected by hydrophilic extracellular and intracellular loops. The majority of the primary sequence homology occurs in the

hydrophobic transmembrane regions with the hydrophilic regions being more diverse. The first receptor for the C-C chemokines that was cloned and expressed binds the chemokines MIP-1α and RANTES. Accordingly, this MIP-1α/RANTES receptor was designated C-C chemokine receptor 1 (also referred to as CCR-1; Neote, K., *et al.*, *Cell*, 72:415-425 (1993); Horuk, R. *et al.*, WO 94/11504, May 26, 1994; Gao, J.-I. *et al.*, *J. Exp. Med.*, 177:1421-1427 (1993)). Three receptors have been characterized which bind and/or signal in response to RANTES: CCR3 mediates binding and signaling of chemokines including eotaxin, RANTES, and MCP-3 (Ponath et al., *J. Exp. Med.*, *183*:2437 (1996)), CCR4 binds chemokines including RANTES, MIP-1α, and MCP-1 (Power, et al., *J. Biol. Chem.*, *270*:19495 (1995)), and CCR5 binds chemokines including MIP-1α, RANTES, and MIP-1β (Samson, *et al.*, *Biochem. 35*: 3362-3367 (1996)). RANTES is a chemotactic chemokine for a variety of cell types, including monocytes, eosinophils, and a subset of T-cells. The responses of these different cells may not all be mediated by the same receptor, and it is possible that the receptors CCR1, CCR4 and CCR5 will show some selectivity in receptor distribution and function between leukocyte types, as has already been shown for CCR3 (Ponath *et al.*). In particular, the ability of RANTES to induce the directed migration of monocytes and a memory population of circulating T-cells (Schall, T. et al., *Nature*, *347*:669-71 (1990)) suggests this chemokine and its receptor(s) may play a critical role in chronic inflammatory diseases, since these diseases are

characterized by destructive infiltrates of T cells and monocytes.

Many existing drugs have been developed as antagonists of the receptors for biogenic amines, for example, as antagonists of the dopamine and histamine receptors. No successful antagonists have yet been developed to the receptors for the larger proteins such as chemokines and C5a. Small molecule antagonists of the interaction between C-C chemokine receptors and their ligands, including RANTES and MIP-1α, would provide compounds useful for inhibiting harmful inflammatory processes "triggered" by receptor ligand interaction, as well as valuable tools for the investigation of receptor-ligand interactions.

## SUMMARY OF THE INVENTION

It has now been found that a class of small organic molecules are antagonists of chemokine receptor function and can inhibit leukocyte activation and/or recruitment. An antagonist of chemokine receptor function is a molecule which can inhibit the binding and/or activation of one or more chemokines, including C-C chemokines such as RANTES and/or MIP-1α, to one or more chemokine receptors on leukocytes and/or other cell types. As a consequence, processes and cellular responses mediated by chemokine receptors can be inhibited with these small organic molecules. Based on this discovery, a method of treating a subject with a disease associated with aberrant leukocyte recruitment and/or activation is disclosed as well as a method of treating a disease mediated by chemokine receptor function. The method comprises administering to the

subject a therapeutically effective amount of a compound or small organic molecule which is an antagonist of chemokine receptor function. Compounds or small organic molecules which have been identified as antagonists of chemokine receptor function are discussed in detail herein below, and can be used for the manufacture of a medicament for treating or for preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also relates to the disclosed compounds and small organic molecules for use in treating or preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also includes pharmaceutical compositions comprising one or more of the compounds or small organic molecules which have been identified herein as antagonists of chemokine function and a suitable pharmaceutical carrier. The invention further relates to novel compounds which can be used to treat an individual with a disease associated with aberrant leukocyte recruitment and/or activation and methods for their preparation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formula (I), (III) and (IV).

Figure 2 is a schematic showing the preparation of representative compounds of Structural Formula (I),(III) and (IV) wherein Z is represented by Structural Formulas (VIII) and wherein Ring A and/or Ring B in Z can be

substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$-, $(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$.

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I), (III) and (IV), wherein Z is represented by Structural Formula (VIII).

Figure 4 is a schematic showing the preparation of compounds represented by Structural Formulas (I) , (III) and (IV), wherein Z is represented by Structural Formula (VIII), wherein W is H.

Figure 5 is a schematic showing the preparation of compounds represented by Structural Formulas (I) , (III) and (IV), wherein Z is represented by Structural Formula (VIII), wherein W is H.

Figure 6 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (VIII) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is one.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (VIII) and wherein Ring A or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is zero.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to small molecule compounds which are modulators of chemokine receptor function. In a preferred embodiment, the small molecule

compounds are antagonists of chemokine receptor function. Accordingly, processes or cellular responses mediated by the binding of a chemokine to a receptor can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{++}]_i$, and/or granule release of proinflammatory mediators.

The invention further relates to a method of treatment, including prophylactic and therapeutic treatments, of a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by the presence of RANTES, MIP-1α, MCP-2, MCP-3 and/or MCP-4 responsive T cells, monocytes and/or eosinophils, including but not limited to diseases such as arthritis (e.g., rheumatoid arthritis), atherosclerosis, arteriosclerosis, ischemia/reperfusion injury, diabetes mellitus (e.g., type 1 diabetes mellitus), psoriasis, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, rejection of transplanted organs and tissues (i.e., acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic treatments) with the methods disclosed herein are inflammatory diseases associated with Human Immunodeficiency Virus (HIV) infection, e.g., AIDS

associated encephalitis, AIDS related maculopapular skin eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation and AIDS related glomerulo nephritis. The method comprises administering to the subject in need of treatment an effective amount of a compound (i.e., one or more compounds) which inhibits chemokine receptor function, inhibits the binding of a chemokine to leukocytes and/or other cell types, and/or which inhibits leukocyte migration to, and/or activation at, sites of inflammation.

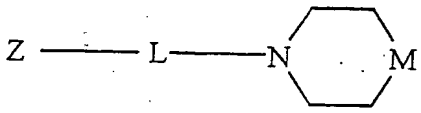
The invention further relates to methods of antagonizing a chemokine receptor, such as CCR1, in a mammal comprising administering to the mammal a compound as described herein.

According to the method, chemokine-mediated chemotaxis and/or activation of pro-inflammatory cells bearing receptors for chemokines can be inhibited. As used herein, "pro-inflammatory cells" includes but is not limited to leukocytes, since chemokine receptors can be expressed on other cell types, such as neurons and epithelial cells.

While not wishing to be bound by any particular theory or mechanism, it is believed that compounds of the invention are antagonists of the chemokine receptor CCR1, and that therapeutic benefits derived from the method of the invention are the result of antagonism of CCR1 function. Thus, the method and compounds of the invention can be used to treat a medical condition involving cells which express CCR1 on their surface and which respond to

signals transduced through CCR1, as well as the specific conditions recited above.

In one embodiment, the antagonist of chemokine receptor function is represented by the structural formula (I):



(I)

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to a pyridine ring and to a carbocyclic aromatic or heteroaromatic ring, wherein each ring in Z is independently substituted or unsubstituted.

L is a $C_1$-$C_{18}$ hydrocarbyl group wherein, optionally one or more of the carbon atoms is replaced by a heteroatom such as nitrogen, oxygen or sulfur.

M is $>NR^2$ or $>CR^1R^2$.

$R^1$ is -H, -OH, $-N_3$, halogen, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$; or $R^1$ can be a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M. $R^1$ is preferably -H or -OH.

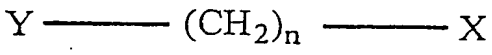
$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group,

an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group. $R^2$ is preferably an aromatic group or a substituted aromatic group.

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

In a preferred embodiment, L in Structural Formula (I) is a chemical group represented by Structural Formula (II):

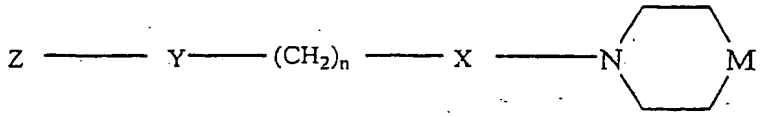


(II)

Y is a covalent bond, -O-, -CO- or =CH-.

n is an integer from one to eighteen, more preferably n is an integer from one to about five, most preferably n is three.

X is a single covalent bond or -CO-, and the antagonist of chemokine receptor function is represented by Structural Formula (III):

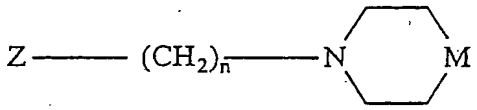


(III)

Z and M are as described above for Structural Formula (I).

Y, n and X are as described above for Structural Formula (II).

In another preferred embodiment, X and Y in Structural Formula (III) are each a covalent bond and the antagonist of chemokine receptor function is a compound represented by Structural Formula (IV):

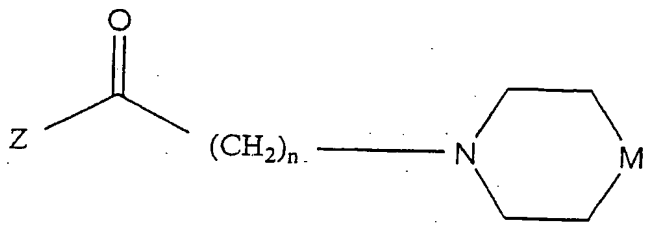


(IV)

n is an integer from one to about five. n is preferably three.

Z and M are as described above for Structural Formula (I).

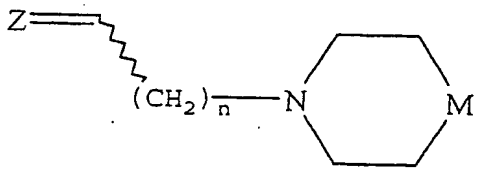
In another preferred embodiment, X is a covalent bond, Y is -CO- and the antagonist of chemokine receptor function is a compound represented by Structural Formula (V):



(V)

Z, M and n are as described above for Structural Formula (IV).

In another preferred embodiment, X is a covalent bond, Y is a double bond and the antagonist of chemokine receptor function is a compound represented by Structural formula (VI):

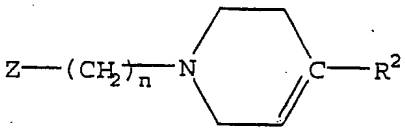


(VI)

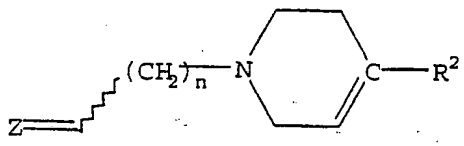
Z, M and n are as described above for Structural Formula (IV). Preferably n is two.

In embodiments where M is $>CR^1R^2$ and $R^1$ is a covalent bond between the carbon atom at M and an adjacent carbon atom in the ring which contains M, the antagonist of

chemokine function can be represented by Structural Formulas (IVa) and (VIa).



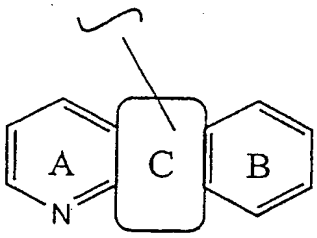
(IVa)



(VIa)

Z, n, and $R^2$ are as described in Structural Formula (I).

Preferably, Z is a tricyclic ring system comprising a six, seven or eight membered cycloalkyl or a non-aromatic heterocyclic ring group fused to a pyridine ring and to a carbocyclic aromatic group. In one example, Z is represented by Structural Formula (VII):




(VII)

The pyridine ring labeled with an "A", and the phenyl ring labeled with a "B" are herein referred to as "Ring A" and "Ring B" respectively. The central ring labeled with a

"C", is herein referred to as "Ring C" and can be, for example, a six, seven or eight membered non-aromatic carbocyclic ring (e.g., a cycloheptane or cyclooctane ring) or a non-aromatic heterocyclic ring. When Ring C is a non-aromatic heterocyclic ring, it can contain one or two heteroatoms such as nitrogen, sulfur or oxygen. When Z is represented by Structural Formula (VII), the tricyclic ring system can be connected to Y in Structural Formula (III) by a single or double covalent bond between Y and a ring atom in Ring C.

Each ring can be unsubstituted or can have one or more substituents. Suitable substituents are as described herein below for substituted aromatic groups. In one example, Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$.

u is zero or one.

t is an integer, such as an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted or unsubstituted.

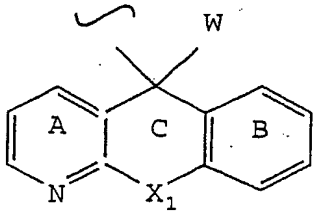
$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a substituted or unsubstituted non-aromatic heterocyclic group. Alternatively, $R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring. In another example, Ring B is substituted with $R^8$ and $R^9$, wherein $R^8$ and $R^9$ are

independently -H, a halogen, alkoxy or alkyl, or, taken together with Ring B, form a naphthyl group

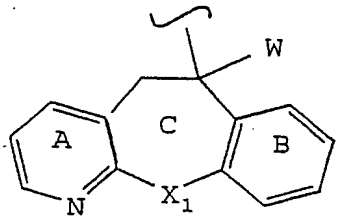
Ring C optionally contains one or more additional substituents as described herein below. Preferably, Ring C is substituted with an electron withdrawing group or is unsubstituted. Suitable electron withdrawing groups include -CN, -CH=NH, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, $-NO_2$ and halogens (e.g., -Br and -Cl). Alternatively, Ring C is substituted with a group selected from $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or -CH2-NHC(O)-O-$R^{11}$.

$R^{11}$ and $R^{12}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, $R^{11}$ and $R^{12}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

Examples of suitable tricyclic ring systems represented by Structural Formula (VII) are provided by Structural Formulas (VIII)-(X), shown below:

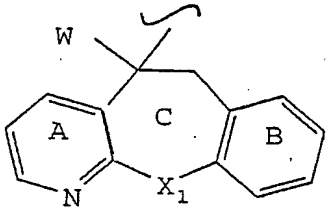



(VIII)




(IX)

and




(X)

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-NR_c-CO-$ or $-CO-NR_c-$.

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzylic group or a substituted benzylic group. In one example, $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$.

s is an integer from zero to about 3; and

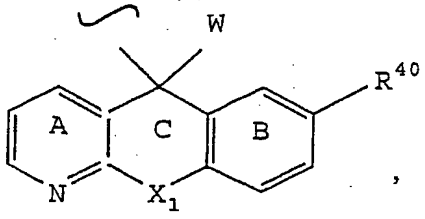
$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, $R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

W is -H, an electron withdrawing group or is selected from $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

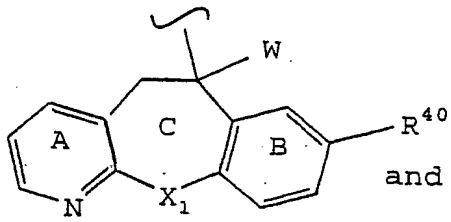
$R^{11}$ and $R^{12}$ are as defined above in Structural Formula (VII).

Ring B in Structural Formulas (VIII)-(X) can be unsubstituted or substituted as described in Structural Formula (VII).

In a preferred embodiment Ring B in Structural Formulas (VIII)-(X) is substituted para to the carbon atom in Ring B which is bonded to $X_1$ in Ring C, and the tricyclic ring system is represented by Structural Formulas (XI)-(XIII) shown below:

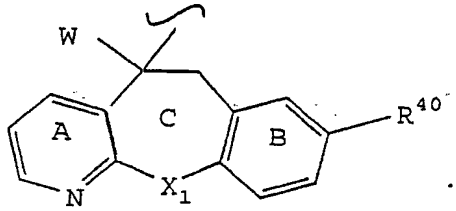



(XI)




and

(XII)

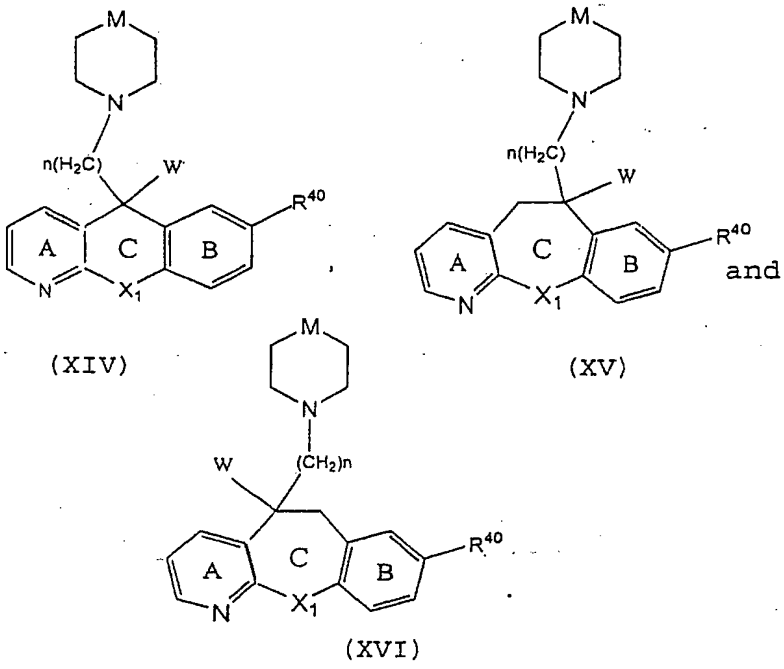



(XIII)

$X_1$ and W are as defined above in Structural Formulas (VIII) - (X).

$R^{40}$ is a substituent as described herein. Preferably $R^{40}$ is an aliphatic group, substituted aliphatic group, -O-(aliphatic group) or -O-(substituted aliphatic group). More preferably $R^{40}$ is an -O-alkyl, such as -O-$CH_3$, -O-$C_2H_5$, -O-$C_3H_7$ or -O-$C_4H_9$.

In this preferred embodiment the antagonist of chemokine receptor function is a compound represented by Structural Formulas (XIV) - (XVI) shown below:



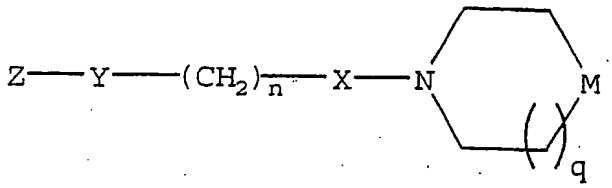

(XIV) (XV) and

(XVI)

n is as defined above in Structural Formula (II). M is as described above in Structural Formula (I).

$X_1$, W and $R^{40}$ are as described above in Structural Formulas (XI) - (XIII). Preferably in Structural Formulas (XIV)-(XVI) $X_1$ is $-CH_2-O-$, W is -CN, M is $>C(OH)R^2$, $R^{40}$ is $-O-CH_3$ and n is three.

In another embodiment, the antagonist of chemokine activity can be represented by Structural Formula (XVII):



(XVII)

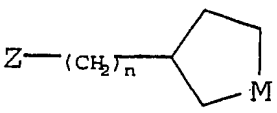
and physiologically acceptable salts thereof.

n, Y, X and M are as described in Structural Formula (I).

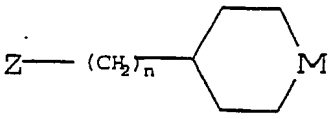
Z is as described herein, preferably Z is as described in Structural Formulas (XI) - (XIII).

q is an integer, such as an integer from zero to about three, and the ring containing M can be substituted or unsubstituted.

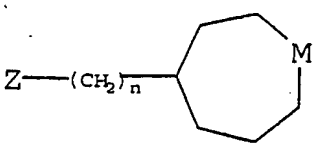
Thus, the antagonist of chemokine function can be represent by, for example, Structural Formulas (XVIIa)-(XVIId):



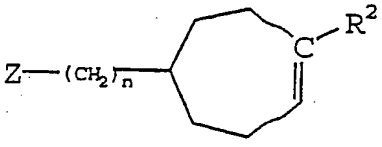
(XVIIa)



(XVIIb)



(XVIIc)



(XVIId)

and physiologically acceptable salts thereof, wherein Z, n and M are as described in Structural Formula (VII), and the ring which contains M is substituted or unsubstituted.

Another embodiment of the invention provides novel compounds employed in these methods.

Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formulas (I) through (XVIId). Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, citric acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium, calcium and the like.

As used herein, aliphatic groups include straight chained, branched or cyclic $C_1$-$C_{20}$ hydrocarbons which are completely saturated or which contain one or more units of unsaturation. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic $C_1$-$C_{20}$ alkyl, alkenyl or alkynyl groups.

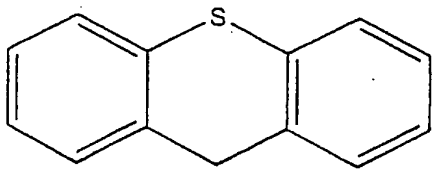
A hydrocarbyl group includes straight chain $C_1$-$C_{18}$ hydrocarbons which are completely saturated or which contain one or more units of unsaturation. Optionally, one

or more of the carbon atoms in a hydrocarbyl group may be replaced with a heteroatom such as oxygen, nitrogen or sulfur. An "alkyl group" is a saturated aliphatic group, as defined above. The term "alkoxy" refers to an alkyl ether chain with an alkyl group. "Alkanoyl" refers to alkyl substituted carbonyl; "aralkanoyl" refers to phenyl-alkyl-CO- and "aroyl" refers to arylcarbonyl including benzoyl, naphthoyl and the like. The term "halogen" means fluoro, chloro, bromo and iodo. The term "substituted phenyl" means phenyl substituted by alkyl, halogen, alkoxy, nitro, amino, acetamido, cyano and trifluoromethyl and naphthyl. "Aralkyl" means $-(CH_2)_x$-aryl, wherein x is an integer from one to four including benzyl.

Aromatic or aryl groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heterocyclic aromatic or heteroaryl groups such as *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Where these rings are fused, for example, to Ring C, the stated point of attachment can be either of the two fused bonds.

Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl

rings. Examples include tetrahydronapthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 1-isoindolyl, 3-isoindolyl, and acridinyl. Also included within the scope of the term "aromatic group", as it is used herein, is a group in which one or more carbocyclic aromatic rings and/or heteroaromatic rings are fused to a cycloalkyl or non-aromatic heterocyclic ring. Examples include decalin, phthalimido, benzodiazepines, benzooxazepines, benzooxazines, phenothiazines, and groups represented by the following structural formulas:



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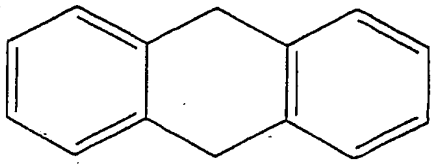
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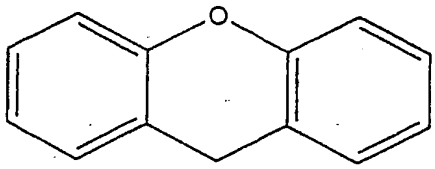

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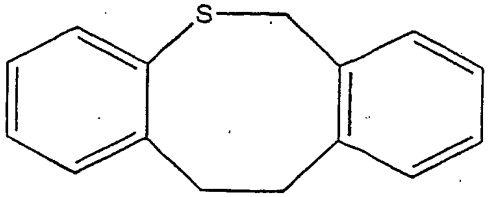

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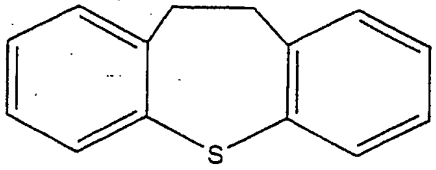

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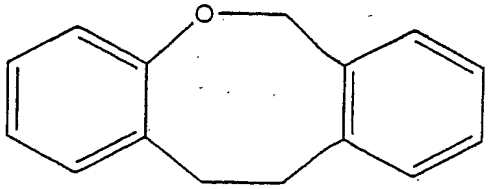
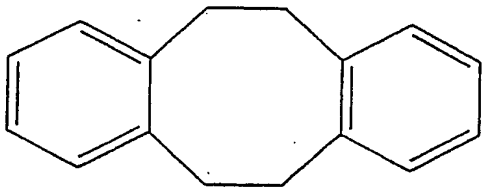


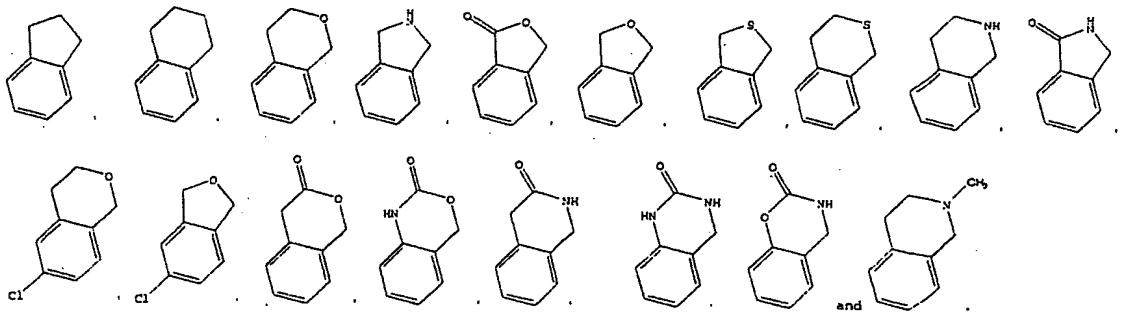
,

or



The term "non-aromatic ring" includes non-aromatic carbocyclic rings and non-aromatic heterocyclic rings. Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered and/or fused to another ring, such as a cycloalkyl or aromatic ring. Examples of non-aromatic rings include, for example,

3-1H-benzimidazol-2-one, 3-1-alkyl-benzimidazol-2-one, 3-1-methyl-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahyrothiophenyl, 3-tetrahyrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidyl, 1-3-alkyl-phthalimidyl, tetrahydronapthyl, benzocyclopentane, benzocyclohexane, benzoxane, benzopyrolidine, benzopiperidine, benzoxolane, benzothiolane, benzothiane,




"Heterocyclic ring" includes "heteroaryl group" and "non-aromatic heterocylic ring". Examples of heterocyclic rings include imidazole, benzimidazole, pyridine, pyrimidine, thiazole, benzothiazole, thienyl, benzothienyl.

Suitable substituents on an alkyl, aliphatic, aromatic, non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, an

aliphatic group, substituted aliphatic group, azido, -OH, a halogen (-Br, -Cl, -I and -F), -O-(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), -CN, $-NO_2$, -COOH, $-NH_2$, -NH(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), -N-(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, -COO(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), $-CONH_2$, -CONH(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group), -CON(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, -SH, $-SO_k$(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group) (k is 0, 1 or 2), $-NH-C(=NH)-NH_2$, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group, and wherein $R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

u is an integer such as zero or one.

t is an integer such as an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted or unsubstituted.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aliphatic or substituted aliphatic group, as a substituent. A substituted alkyl or aliphatic group can also have a non-aromatic heterocyclic ring, benzyl, substituted benzyl, aromatic or substituted aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent.

Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl and aromatic sulfonyl.

Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, $-NO_2$ and halogens.

The compounds disclosed herein may be obtained as different sterioisomers (e.g., diastereomers and enantiomers). For example, when the antagonist of chemokine receptor function is represented by Structural Formula (III) and Z is represented by Structural Formula (VII), the carbon atom in Ring C which is bonded to Y may be in the R or S sterioconfiguration. It is pointed out that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and a method of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures.

It is understood that one sterioisomer can have greater activity than another, The desired isomer can be determined by screening for activity, employing the methods described herein.

In the structural formulas depicted herein, the single or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:

For example, the corresponding symbol in Structural Formula (VIII) or (IX) indicates that the tricyclic ring system, which represent Z in Structural Formula (IV), is connected to the alkylene group in Structural Formula (IV) by a single covalent bond between the alkylene group and the ring carbon in Ring C which is bonded to W.

A "subject" is preferably a bird or a mammal, such as a human, but can also be an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, fowl, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

An "effective amount" of a compound is an amount which results in the inhibition of one or more processes mediated by the binding of a chemokine to a receptor in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Examples of such processes include leukocyte migration, integrin activation, transient

increases in the concentration of intracellular free calcium $[Ca^{2+}]_i$ and granule release of proinflammatory mediators. Alternatively, an "effective amount" of a compound is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compound can range from about 0.1 mg per day to about 100 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day. An antagonist of chemokine receptor function can also be administered in combination with one or more additional therapeutic agents, e.g. theophylline, β-adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone) and the like.

The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example,

systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), transdermally, topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral or parenteral administration are preferred modes of administration.

The compound can be administered to the individual in conjunction with an acceptable pharmaceutical or physiological carrier as part of a pharmaceutical composition for treatment of HIV infection, inflammatory disease, or the other diseases discussed above. Formulation of a compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable carriers may contain inert ingredients which do not interact with the compound. Standard formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, et al., "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

The activity of compounds of the present invention can be assessed using suitable assays, such as receptor binding assays and chemotaxis assays. For example, as described in the Exemplification Section, small molecule antagonists of RANTES and MIP-1α binding have been identified utilizing THP-1 cells which bind RANTES and chemotax in response to RANTES and MIP-1α as a model for leukocyte chemotaxis. Specifically, a high through-put receptor binding assay, which monitors $^{125}$I-RANTES and $^{125}$I-MIP-1α binding to THP-1 cell membranes, was used to identify small molecule antagonists which block binding of RANTES and MIP-1α. Compounds of the present invention can also be identified by virtue of their ability to inhibit the activation steps triggered by binding of a chemokine to its receptor, such as chemotaxis, integrin activation and granule mediator release. They can also be identified by virtue of their ability to block RANTES and MIP-1α mediated HL-60, T-cell, peripheral blood mononuclear cell, and eosinophil chemotactic response.

The compounds disclosed herein can be prepared accordingly to the schemes shown in Figures 1-5. The schemes are described in greater detail below.

Figure 1 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is CN.

$L^1$, $L^2$ and $L^3$ in Figure 1 are suitable leaving groups such as halogen; p-toluene sulfonate, mesylate, alkoxy and phenoxy. The other symbols are as defined above.

The reduction reaction in Step 1 of Figure 1 is performed with a reducing agent such as sodium borohydride or lithium aluminum hydride (LAH) in an inert solvent such as methanol or tetrahydrofuran (THF). The reaction is carried out at temperatures ranging from 0°C up to the reflux temperature and for 5 minutes to 72 h.

Compounds represented by formula II in Figure 1 can be prepared by procedures disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081, the entire teachings of which are incorporated herein by reference.

A chlorination reaction in step 2 of Figure 1 can be performed with reagents such as thionyl chloride. The reaction can be carried out in an inert solvent such as methylene chloride at 0°C up to the reflux temperature for 5 minutes to 72 h. The hydroxy group can be also be converted to other leaving groups by methods familiar to those skilled in the art.

The cyanation reaction in step 3 of Figure 1 can be carried out using reagents such as copper cyanide, silver cyanide or sodium cyanide in an inert solvent such as benzene or toluene. Reaction temperatures range from 0°C up to the reflux temperature for 5 minutes to 72 h. Compounds represented by Formula V in Figure 1 can also be prepared by the procedures described in J. Med. Chem. 1994, 37, 804-810 and U.S. Patent 5672611, the entire teachings of which are incorporated herein by reference.

The alkylation reactions in steps 4 and 5 of Figure 1 can be carried out in a solvent such as acetone, methyl ethyl

ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide (when necessary). The reaction temperature can range from room temperature up to the reflux temperature and for 5 minutes to 72 h.

The product of the synthetic scheme shown in Figure 1 can be decyanated using a reducing agent such as lithium aluminum hydride (LAH) in an inert solvent such as ether or tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 2 is a schematic showing the preparation of representative compounds of Structural Formula (I), (III) and (IV), wherein Z is represented by Structural Formula (VIII) and wherein Ring A and/or Ring B in Z can be substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

In Figure 2, the hydrolysis reaction may be carried out in a mixture of aqueous alkali metal hydroxide solution and a solvent such as methanol, ethanol, tetrahydrofuran (THF) or dioxane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. The acylation reaction can be carried out using dicyclohexylcarbodiimide (DCC) or (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (DEC) in a solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or methylene chloride in the presence of a base such as pyridine or triethylamine (when necessary) at temperatures of 0 to 100°C for 5 minutes to 72 h.

Compounds represented by Structural Formulas (I), (III) and (IV) wherein Z is represented by Structural Formulas (VIII)-(XI), wherein $X_1$ is -CO-N($R_c$)- and $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$ can be prepared by suitable modification of the scheme shown in Figures 1 and 2. One modification utilizes the starting material shown in Figures 1 and 2, wherein $X_1$ is -CO-NH-. The amide is then alkylated with $L^3-(CH_2)_s-COOR^{30}$ using the alkylation procedures described above. $L^3$ is a suitable leaving group. The remainder of the synthesis is as described in Figures 1 and 2.

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I), (III) and (IV) wherein Z is represented by Structural Formula (VIII).

The reduction of the cyano group to an amine in Figure 3 can be carried out using metal hydrides or by catalytic reduction processes. Suitable reducing agents include lithium aluminum hydride (LAH), diisobutyl aluminum hydride (DIBAL-H), borane-methyl sulfide complex or sodium borohydride. The reduction can be carried out in an inert solvent such as ether, tetrahydrofuran (THF), methylene chloride or methanol at -78°C up to the reflux temperature for 5 minutes to 72 h. It is also possible to isolate the corresponding imine intermediate, which can be converted to the amine using similar reduction processes.

Figure 4 is a schematic showing the preparation of compounds represented by Structural Formulas (I), (III) and (IV), wherein Z is represented by Structural Formula

(VIII), wherein W is H. The reduction of the double bond in step 1 of Figure 4 can be carried out using the catalytic reduction process. Suitable catalyst include palladium-carbon, platinum oxide or Ranney-nickel. The reduction can be carried out in an inert solvent such as methanol, ethanol or acetic acid at temperatures of 0 to 70°C under a hydrogen pressure of 1 to 100 atm for 5 minuets to 72 h. The alkylation reactions in step 2 of Figure 4 can be carried out using the same as those in step 5 of Figure 1.

Figure 5 is a schematic showing the preparation of compounds represented by Structural Formulas (I), (III) and (IV), wherein Z is represented by Structural Formula (VIII), wherein W is H. The alkylation reaction in step 1 of Figure 5 can be carried out using the same as those in step 5 of Figure 1. The reduction of the double bond in step 2 of Figure 5 can be carried out using the same as those in step 1 of Figure 4.

Figure 6 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (VIII) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is one. In Figure 6, the alkylation reaction can be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the

reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (VIII) and wherein Ring A or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is zero. L4 is a suitable leaving group such as halogen or trifluoromethylsulfonate. In Figure 7, a palladium coupling reaction such as Stille coupling, Suzuki coupling, Heck reaction, or carboxylation using carbon monoxide can be carried out using a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium chloride, and palladium acetate in a solvent such as tetrahydrofuran (THF), 1,4-dioxane, toluene, dimethylformamide (DMF), or dimethylsufoxide (DMSO) in the presence of additive (when necessary) such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine, sodium bicarbonate, tetraethylammonium chloride, or lithium chloride at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Although Figures 1-7 show the preparation of compounds in which B is a phenyl ring, analogous compounds with heteroaryl groups for Ring B can be prepared by using the starting materials with heteroaryl groups in the corresponding positions, which can be prepared according to methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-propyl]piperidin-4-ol

Step 1

To a solution of 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one (5.0g) in THF (50ml) was added 1.1M cyclopropylmagnesium bromide THF solution (25ml) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was filtered and washed with ethyl acetate-hexane (1:2) to give 5-cyclopropyl-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-ol (5.0g).

Step 2

To a solution of the product of step 1 (4.3g) in acetic acid (30ml) was added 48% aqueous HBr (25ml) at 10°C. The reaction mixture was warmed to room temperature, and stirred for 12 hours. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over

magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5-(3-bromopropylidene)-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepine (5.6g).

$^1$H-NMR ($CDCl_3$) δ: 2.74(2H,q), 3.46(2H,t), 3.78(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82(3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd).

Step 3

To a solution of the product of step 2 (160mg) in ethanol (3ml) and acetic acid (1ml) were added 10% Pd-C (79mg) was stirred under hydrogen (under a balloon) at room temperature for 24 hour. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by preparative thin layer chromatography eluting with ethyl acetate-hexane (1:2) to give 5-(3-bromopropyl)-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepine (48mg).

$^1$H-NMR ($CDCl_3$) δ: 1.80-2.45(4H,m), 3.33-3.39(2H,m), 3.59(1h,dd), 3.77(3H,s), 4.98(1H,d), 5.44(1H,d), 6.70-6.79(2H,m), 7.08-7.14(5H,m), 7.52(1H,dd), 8.41(1H,dd).

Step 4

To a solution the product of step 3 (45mg) in DMF (1ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (54mg) and potassium carbonate (19mg) and the mixture was stirred at 50°C for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was

separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (10:1) to give the titled compound (19mg). $^1$H-NMR ($CDCl_3$) δ: 1.50(1H,brs), 1.67-1.72(2H,m), 2.00-2.47(10H,m), 2.76-2.81(2H,m), 3.59(1H,dd), 3.77(3H,s), 4.97(1H,d), 5.43(1H,d), 6.72-6.78(2H,m), 7.06-7.13(2H,m), 7.26-7.44(4H,m), 7.52(1H,dd), 8.37(1H,dd).
MS m/z: 479(M+1)

Examples 2 - 157 which can be represented by Structural Formulas (XIV) and (XVI) and are presented in Table 1 and Table 1a, can be prepared by methods set forth in the schemes in Figure 1-5 and the procedures described above.

Table 1

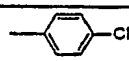
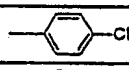
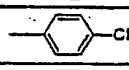
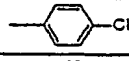
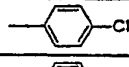
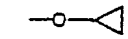
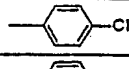
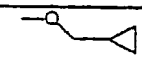
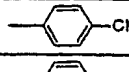
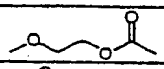
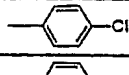
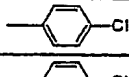
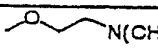
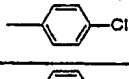
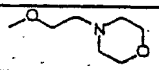
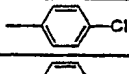
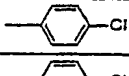
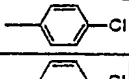
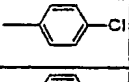
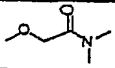
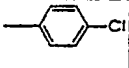
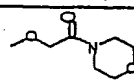
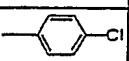
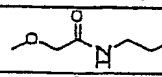
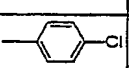
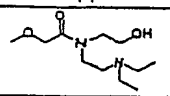
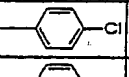
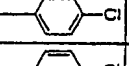
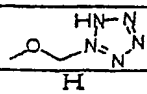
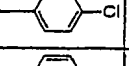
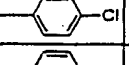
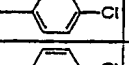
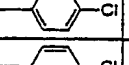
| Example | $X_1$ | W | M | $R^1$ | $R^2$ | $R^{40}$ |
|---|---|---|---|---|---|---|
| 2 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | -OH |
| 3 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CH_3$ |
| 4 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CH_2CH_3$ |
| 5 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OCH(CH_3)_2$ |
| 6 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 7 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 8 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 9 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 10 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 11 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 12 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CN$ |
| 13 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CO_2CH_2CH_3$ |
| 14 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CO_2H$ |
| 15 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 16 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 17 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 18 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 19 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OC(CH_3)_2CO_2CH_2CH_3$ |
| 20 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | $-OC(CH_3)_2CO_2H$ |
| 21 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  |  |
| 22 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | H |
| 23 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | F |
| 24 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | Cl |
| 25 | $-CH_2-O-$ | -H | $CR^1R^2$ | -OH |  | Br |

Table 1 (cont.)

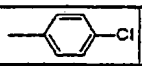
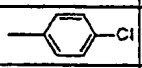
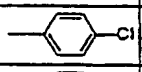
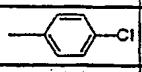
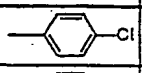
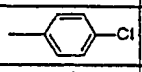
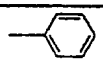
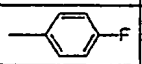
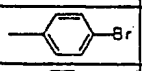
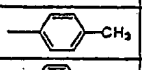
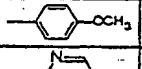
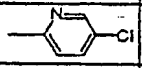
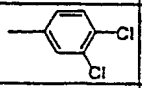
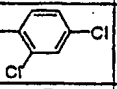
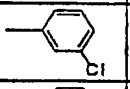
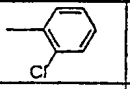
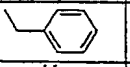
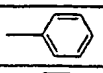
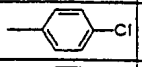
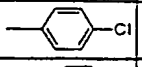
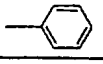
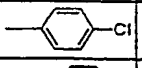
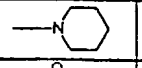
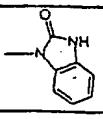
| | | | | | | |
|---|---|---|---|---|---|---|
| 26 | -CH2-O- | -H | CR'R" | -OH |  | $CH_3$ |
| 27 | -CH2-O- | -H | CR'R" | -OH |  | $-CO_2H$ |
| 28 | -CH2-O- | -H | CR'R" | -OH |  | $-CH_2CO_2CH_3$ |
| 29 | -CH2-O- | -H | CR'R" | -OH |  | $-CH_2CO_2H$ |
| 30 | -CH2-O- | -H | CR'R" | -OH |  | $-CH_2CH_2CO_2H$ |
| 31 | -CH2-O- | -H | CR'R" | -OH |  | $-CH_2CH_2CH_2CO_2H$ |
| 32 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 33 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 34 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 35 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 36 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 37 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 38 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 39 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 40 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 41 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 42 | -CH2-O- | -H | CR'R" | -OH |  | $-OCH_3$ |
| 43 | -CH2-O- | -H | CR'R" | -OH | H | $-OCH_3$ |
| 44 | -CH2-O- | -H | CR'R" | -CN |  | $-OCH_3$ |
| 45 | -CH2-O- | -H | CR'R" | $-OCH_3$ |  | $-OCH_3$ |
| 46 | -CH2-O- | -H | CR'R" | $-OCOCH_3$ |  | $-OCH_3$ |
| 47 | -CH2-O- | -H | CR'R" | -H |  | $-OCH_3$ |
| 48 | -CH2-O- | -H | CR'R" | -H |  | $-OCH_3$ |
| 49 | -CH2-O- | -H | CR'R" | -H |  | $-OCH_3$ |
| 50 | -CH2-O- | -H | CR'R" | -H |  | $-OCH_3$ |

Table 1 (cont.)

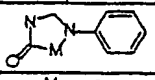
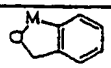
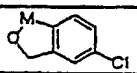
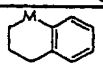
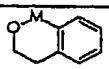
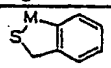
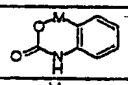
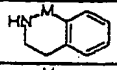
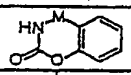
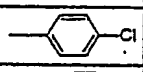
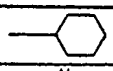
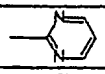
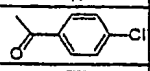
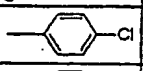
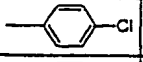
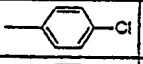
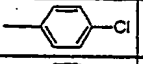
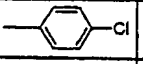
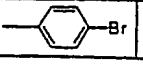
| Example | $X_1$ | W | M | $R^1$ | $R^2$ | $R^{40}$ |
|---|---|---|---|---|---|---|
| 51 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 52 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 53 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 54 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 55 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 56 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 57 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 58 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 59 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 60 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 61 | -CH2-O- | -H | $CR^1R^2$ | |  | $-OCH_3$ |
| 62 | -CH2-O- | -H | $NR^2$ | |  | $-OCH_3$ |
| 63 | -CH2-O- | -H | $NR^2$ | |  | $-OCH_3$ |
| 64 | $-CH_2-O-$ | -H | $NR^2$ | |  | $-OCH_3$ |
| 65 | $-CH_2-O-$ | -H | $NR^2$ | |  | $-OCH_3$ |
| 66 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 67 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_2CH_3$ |
| 68 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_2CN$ |
| 69 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_2CO_2CH_2CH_3$ |
| 70 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_2CO_2H$ |
| 71 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | H |
| 72 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-CH_2CO_2H$ |
| 73 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_3$ |

Table 1 (cont.)

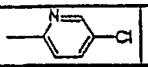
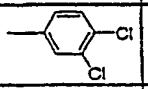
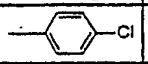
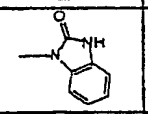
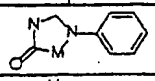
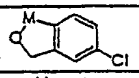
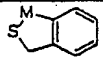
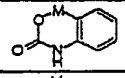
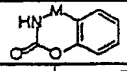
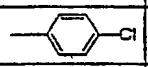
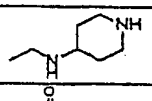
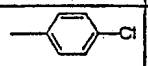
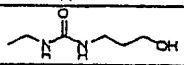
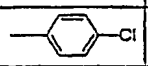
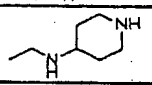
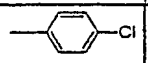
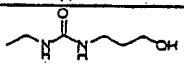
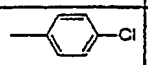
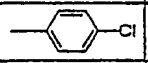
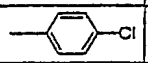
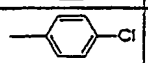
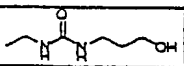
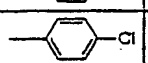
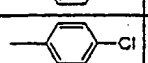
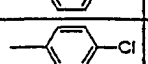
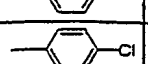
| | | | | | | |
|---|---|---|---|---|---|---|
| 74 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 75 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 76 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -H |  | $-OCH_3$ |
| 77 | $-CH_2-O-$ | -CN | $CR^1R^2$ | -H |  | $-OCH_3$ |
| 78 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 79 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 80 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 81 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 82 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 83 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 84 | $-CH_2-O-$ | -CN | $CR^1R^2$ |  | | $-OCH_3$ |
| 85 | $-CH_2-O-$ | -CN | $NR^2$ | |  | $-OCH_3$ |
| 86 | $-CH_2-O-$ |  | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 87 | $-CH_2-O-$ |  | $CR^1R^2$ | -OH |  | $-OCH_2CH_3$ |
| 88 | $-CH_2-O-$ |  | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 89 | $-CH_2-O-$ |  | $CR^1R^2$ | -OH |  | $-OCH_2CH_3$ |
| 90 | $-CH_2-S-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 91 | $-CH_2-S-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CH_3$ |
| 92 | $-CH_2-S-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 93 | $-CH_2-S-$ |  | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 94 | $-CH_2CH_2-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_3$ |
| 95 | $-CH_2CH_2-$ | -H | $CR^1R^2$ | -OH |  | $-OCH_2CH_3$ |
| 96 | $-CH_2CH_2-$ | -CN | $CR^1R^2$ | -OH |  | $-OCH_3$ |

Table 1 (cont.)

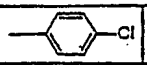
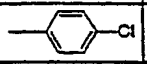
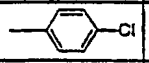
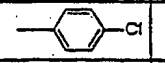
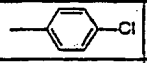
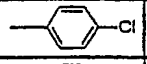
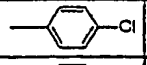
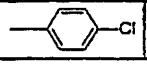
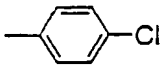
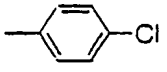
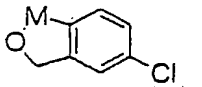
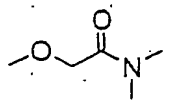
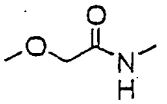
| | | | | | | |
|---|---|---|---|---|---|---|
| 97 | -CH=CH- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 98 | -CO-NH- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 99 | -CO-NCH$_3$- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 100 | -NH-CO- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 101 | -NCH$_3$-CO- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 102 | -CH$_2$-NH- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 103 | -CH$_2$-NCH$_3$- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 104 | -NH-CH$_2$- | -H | CR'R" | -OH |  | -OCH$_3$ |
| 105 | -NCH$_3$- CH$_2$- | -H | CR'R" | -OH |  | -OCH$_3$ |

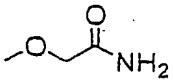
Table 1a

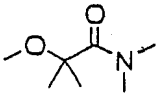
| Example | X1 | W | M | $R^1$ | $R^2$ | $R^{40}$ |
|---|---|---|---|---|---|---|
| 106 | -CH2-O- | -H | CR1R2 | -OH | | -OCH2CH2OH |
| 107 | -CH2-O- | -H | CR1R2 | -OH | | -OCH2CH2OCH3 |
| 108 | -CH2-O- | -H | CR1R2 | -OH | | B |
| 109 | -CH2-O- | -H | CR1R2 | -OH | | C |
| 110 | -CH2-O- | -H | CR1R2 | -OH | | D |
| 111 | -CH2-O- | -H | CR1R2 | -OH | | E |
| 112 | -CH2-O- | -H | CR1R2 | -OH | | F |
| 113 | -CH2-O- | -H | CR1R2 | -H | | -OH |
| 114 | -CH2-O- | -H | CR1R2 | -H | | -OCH2CH2OH |
| 115 | -CH2-O- | -H | CR1R2 | -H | | -OCH2CH2OCH3 |
| 116 | -CH2-O- | -H | CR1R2 | -H | | A |
| 117 | -CH2-O- | -H | CR1R2 | -H |  | C |
| 118 | -CH2-O- | -H | CR1R2 | -H | | D |
| 119 | -CH2-O- | -H | CR1R2 | -H | | F |
| 120 | -CH2-O- | CN | CR1R2 | -OH | | -OCH2CH2OH |
| 121 | -CH2-O- | -CN | CR1R2 | -OH | | -OCH2CH2OCH3 |
| 122 | -CH2-O- | -CN | CR1R2 | -OH | | B |
| 123 | -CH2-O- | -CN | CR1R2 | -OH | | C |
| 124 | -CH2-O- | -CN | CR1R2 | -OH | | D |
| 125 | -CH2-O- | -CN | CR1R2 | -OH | | E |
| 126 | -CH2-O- | -CN | CR1R2 | -OH | | F |
| 127 | -CH2-O- | -CN | CR1R2 | -H | | -OH |
| 128 | -CH2-O- | -CN | CR1R2 | -H | | -OCH2CH2OH |
| 129 | -CH2-O- | -CN | CR1R2 | -H | | -OCH2CH2OCH3 |
| 130 | -CH2-O- | -CN | CR1R2 | -H | | A |
| 131 | -CH2-O- | -CN | CR1R2 | -H | | C |
| 132 | -CH2-O- | -CN | CR1R2 | -H | | D |
| 133 | -CH2-O- | -CN | CR1R2 | -H | | F |
| 134 | -CH2-O- | -H | CR1R2 | | | -OH |
| 135 | -CH2-O- | -H | CR1R2 | | | -OCH2CH2OH |
| 136 | -CH2-O- | -H | CR1R2 | | | -OCH2CH2OCH3 |
| 137 | -CH2-O- | -H | CR1R2 | | | A |
| 138 | -CH2-O- | -H | CR1R2 | | | C |
| 139 | -CH2-O- | -H | CR1R2 | | | D |
| 140 | -CH2-O- | -H | CR1R2 | | | F |
| 141 | -CH2-O- | -CN | CR1R2 | | | -OH |
| 142 | -CH2-O- | -CN | CR1R2 | | | -OCH2CH2OH |
| 143 | -CH2-O- | -CN | CR1R2 | | | -OCH2CH2OCH3 |
| 144 | -CH2-O- | -CN | CR1R2 | | | A |
| 145 | -CH2-O- | -CN | CR1R2 | | | C |
| 146 | -CH2-O- | -CN | CR1R2 | | | D |
| 147 | -CH2-O- | -CN | CR1R2 | | | F |
| 148 | -CH2-CH2- | -H | CR1R2 | -OH | | -OCH2CH2OH |
| 149 | -CH2-CH2- | -CN | CR1R2 | -OH | | F |
| 150 | -CH2-CH2- | -H | CR1R2 | -OH | | -OCH2CH2OH |
| 151 | -CH2-CH2- | -CN | CR1R2 | -OH | | F |
| 152 | -CH2-S- | -H | CR1R2 | -OH |  | -OCH2CH2OH |
| 153 | -CH2-S- | -CN | CR1R2 | -OH | | F |
| 154 | -CH2-S- | -H | CR1R2 | -OH | | -OCH2CH2OH |
| 155 | -CH2-S- | -CN | CR1R2 | -OH | | F |
| 156 | -CH2-O- | -H | CR1R2 | -OH | | G |
| 157 | -CH2-O- | -CN | CR1R2 | -OH | | G |

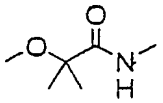

(example 80)

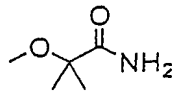
A 

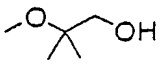
B 

C 

D 

E 

F 

G 

Example 158

Membrane Preparations for Chemokine Binding and Binding Assays

Membranes are prepared from THP-1 cells (ATCC #TIB202). Cells are harvested by centrifugation, washed twice with PBS (phosphate-buffered saline), and the cell pellets are frozen at -70 to -85°C. The frozen pellet is thawed in ice-cold lysis buffer consisting of 5 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid) pH 7.5, 2 mM EDTA (ethylenediaminetetraacetic acid), 5 μg/ml each aprotinin, leupeptin, and chymostatin (protease inhibitors), and 100 μg/ml PMSF (phenyl methane sulfonyl fluoride - also a protease inhibitor), at a concentration of 1 to 5 x $10^7$ cells/ml. This procedure results in cell lysis. The suspension is mixed well to resuspend all of the frozen cell pellet. Nuclei and cell debris are removed by centrifugation of 400 x g for 10 minutes at 4°C. The supernatant is transferred to a fresh tube and the membrane fragments are collected by centrifugation at 25,000 x g for 30 minutes at 4°C. The supernatant is aspirated and the pellet is resuspended in freezing buffer consisting of 10 mM HEPES pH 7.5, 300 mM sucrose, 1μg/ml each aprotinin, leupeptin, and chymostatin, and 10 μg/ml PMSF (approximately 0.1 ml per each $10^8$ cells). All clumps are resolved using a minihomogenizer, and the total protein concentration is determined using a protein assay kit (Bio-Rad, Hercules, CA, cat #500-0002). The membrane solution is then aliquoted and frozen at -70 to -85°C until needed.

Binding Assays utilize the membranes described above. Membrane protein (2 to 20 μg total membrane protein) is incubated with 0.1 to 0.2 nM $^{125}$I-labeled RANTES or MIP-1α with or without unlabeled competitor (RANTES or MIP-1α) or various concentrations of compounds. The binding reactions are performed in 60 to 100 μl of a binding buffer consisting of 10 mM HEPES pH 7.2, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% BSA (bovine serum albumin), for 60 min at room temperature. The binding reactions are terminated by harvesting the membranes by rapid filtration through glass fiber filters (GF/B or GF/C, Packard) which are presoaked in 0.3% polyethyleneimine. The filters are rinsed with approximately 600 μl of binding buffer containing 0.5 M NaCl, dried, and the amount of bound radioactivity is determined by scintillation counting in a Topcount beta-plate counter.

The activities of test compounds can be reported as $IC_{50}$ values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using $^{125}$I-RANTES or $^{125}$MIP-1α as ligand and THP-1 cell membranes. Specific binding can be defined as the total binding minus the non-specific binding; non-specific binding can be the amount of cpm still detected in the presence of excess unlabeled RANTES or $^{125}$MIP-1α.

Table 2

BIOLOGICAL DATA

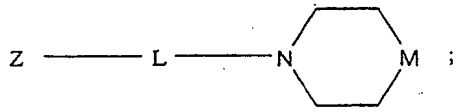
| Example | $IC_{50}$ ($\mu$M) |
|---|---|
| 1 | <1 |

Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof a therapeutically effective amount of a compound represented by the following structural formula:




and physiologically acceptable salts thereof, wherein:

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to a pyridine ring and to a carbocyclic aromatic or heteroaromatic ring, wherein each ring in Z is independently substituted or unsubstituted;

L is a $C_1$-$C_{18}$ substituted or unsubstituted hydrocarbyl group;

M is $>NR^2$ or $>CR^1R^2$;

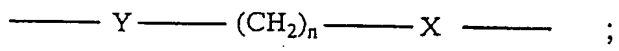
$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; and

$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

2. The method of Claim 1 wherein L is represented by the following structural formula:



wherein:

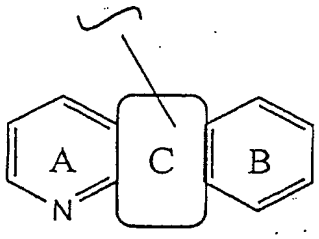
Y is a single or double covalent bond, -O-, -CO- or =CH-;

n is an integer from one to about five; and

X is a covalent bond or -CO-.

3. The method of Claim 2 wherein X and Y are each a covalent bond.

4. The method of Claim 3 wherein Z is represented by the following structural formula:



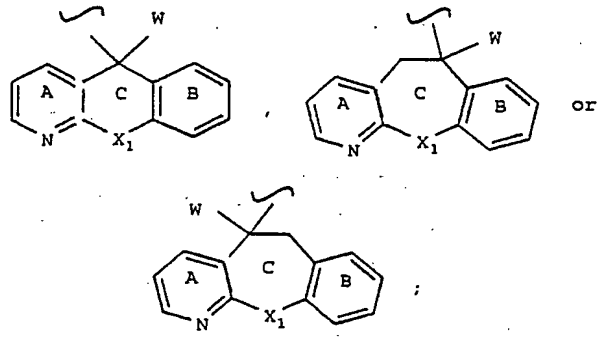
;

wherein:

Ring A and Ring B are individually substituted or unsubstituted; and

Ring C is a substituted or unsubstituted $C_6$, $C_7$ or $C_8$ non-aromatic carbocyclic ring or a substituted or unsubstituted non-aromatic heterocyclic ring.

5. The method of Claim 4 wherein Z is represented by a structural formula selected from:



wherein:

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$ or $-CO-NR_c-$ ;

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group;

W is -H, an electron withdrawing group, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, -CH=NH, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$; wherein:

$R^{11}$ and $R^{12}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{11}$ and $R^{12}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

n is an integer from 2-5;

Ring B is substituted with $R_8$ and $R_9$, wherein $R_8$ and $R_9$ are independently -H, a halogen, alkoxy or alkyl, or, taken together with Ring B, form a naphthyl group;

M is >N(alkanoyl), >N(aroyl), >N(aralkoyl), >N(alkyl), >N(aralkyl), >N(cycloalkyl), >C(OH)(aryl) or >CH(heteroaryl).

6. The method of Claim 5 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

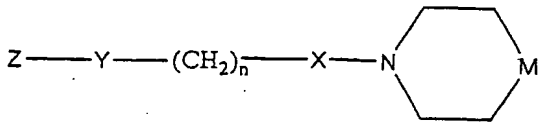
s is an integer from zero to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

7. The method of Claim 2 wherein X is a covalent bond and Y is -CO-.

8. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof a therapeutically effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about five;

X is a single covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

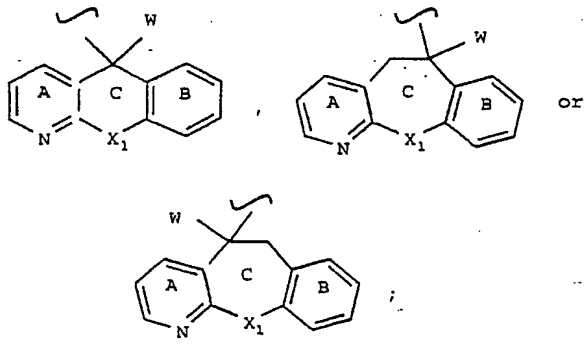
$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; and

$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:




wherein:

Ring B and Ring C are independently substituted or unsubstituted;

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$, $-CO-NR_c-$ ;

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

W is -H or an electron withdrawing group .

9. The method of Claim 8 wherein Ring B is substituted with -OH, a halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

10. The method of Claim 8 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

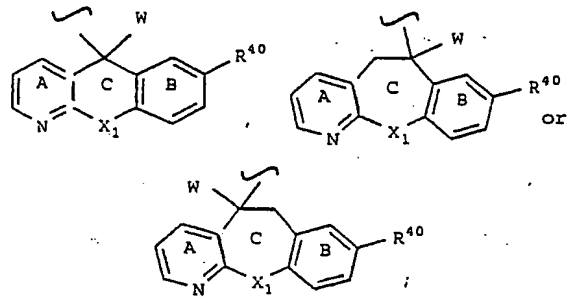
s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

11. The method of Claim 9 wherein Ring B is substituted para to the carbon atom of Ring B which is bonded to $X_1$

in Ring C, and Z represented by a structural formula selected from:




wherein $R^{40}$ is -OH, halogen, aliphatic group, substituted aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

12. The method of Claim 11 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

13. The method of Claim 11 wherein $R^{40}$ $-O-CH_3$.

14. The method of Claim 13 wherein $R^1$ is -OH.

15. The method of Claim 13 wherein M is $>C(OH)R^2$ and n is three.

16. The method of Claim 15 wherein:

W is -CN; and

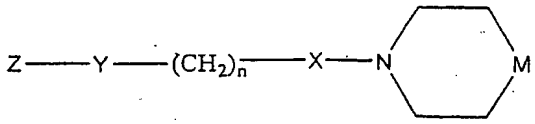
$X_1$ is $-CH_2-O-$, $-CH_2-CH_2-$ or $-CH_2-S-$.

17. The method of Claim 16 wherein $R^2$ is a substituted or unsubstituted aromatic group.

18. The method of Claim 17 wherein $R^2$ is an aromatic group that is substituted with a halogen.

19. The method of Claim 18 wherein $R^2$ is a 4-chlorophenyl group.

20. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof a therapeutically effective amount of a compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about five;

X is a single covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; and

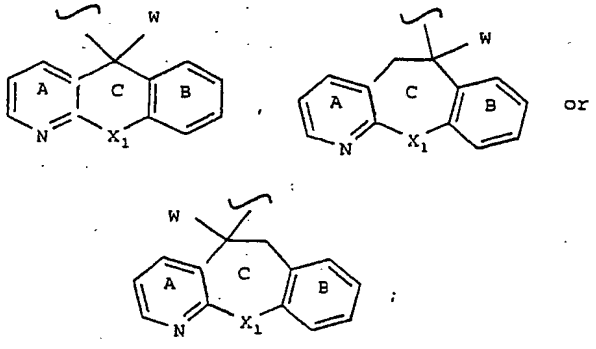
$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a

substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:




wherein:

Ring B and Ring C are independently substituted or unsubstituted;

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$, $-CO-NR_c-$ ;

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

W is $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

$R^{11}$ and $R^{12}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{11}$ and $R^{12}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

21. The method of Claim 20 wherein Ring B is substituted with -OH, a halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

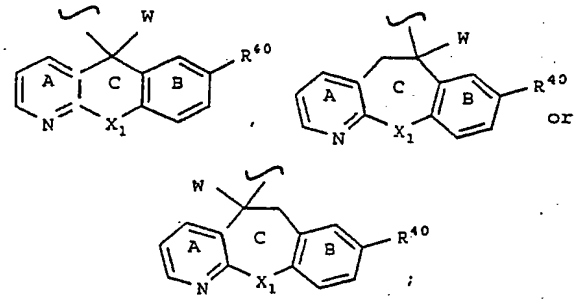
22. The method of Claim 20 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

23. The method of Claim 21 wherein Ring B is substituted para to the carbon atom of Ring B which is bonded to $X_1$ in Ring C, and Z is represented by a structural formula selected from:



wherein $R^{40}$ is -OH, halogen, aliphatic group, substituted aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$,

$-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

24. The method of Claim 23 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

25. The method of Claim 23 wherein $R^{40}$ is $-O-CH_3$.

26. The method of Claim 25 wherein $R^1$ is -OH.

27. The method of Claim 25 wherein M is $>C(OH)R^2$ and n is three.

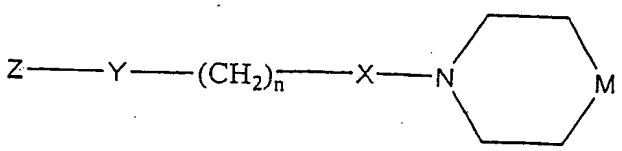
28. The method of Claim 27 wherein $X_1$ is $-CH_2-O$, $-CH_2-CH_2-$ or $-CH_2-S-$.

29. The method of Claim 28 wherein $R^2$ is a substituted or unsubstituted aromatic group.

30. The method of Claim 29 wherein $R^2$ is an aromatic group that is substituted with a halogen.

31. The method of Claim 30 wherein $R^2$ is a 4-chlorophenyl group.

32. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof a therapeutically effective amount of a compound represented by the following structural formula:




;

and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about five;

X is a single covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH,

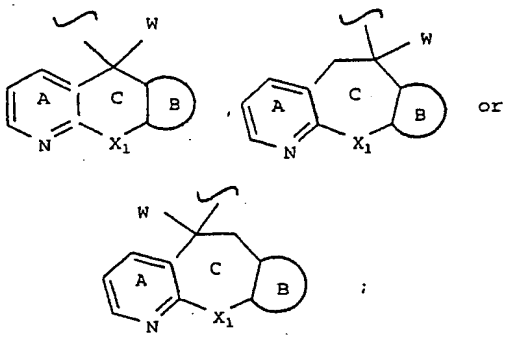
-S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, -CO-$NR^3R^4$ or -$NR^3R^4$; and

$R^2$ is -H, -OH, an acyl group, a substituted acyl group, -$NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



wherein:

Ring B is a substituted or unsubstituted carbocyclic aromatic or heteroaryl group;

$X_1$ is a covalent, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-NR_c-CO-$ or $-CO-NR_c-$ ; wherein:

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

W is -H, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$, $-CH_2-NHC(O)-O-R^{11}$ or an electron withdrawing group;

$R^{11}$ and $R^{12}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{11}$ and $R^{12}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

33. The method of Claim 32 wherein Ring B is substituted with -OH, a halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

34. The method of Claim 32 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

35. The method of Claim 32 wherein $R^1$ is -OH.

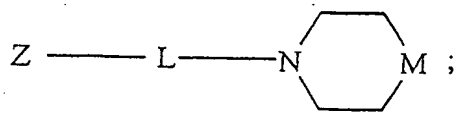
36. The method of Claim 32 wherein M is $>C(OH)R^2$ and n is three.

37. The method of Claim 36 wherein $R^2$ is a substituted or unsubstituted aromatic group.

38. The method of Claim 37 wherein $R^2$ is an aromatic group that is substituted with a halogen.

39. The method of Claim 38 wherein $R^2$ is a 4-chlorophenyl group.

40. A compound represented by the following structural formula:

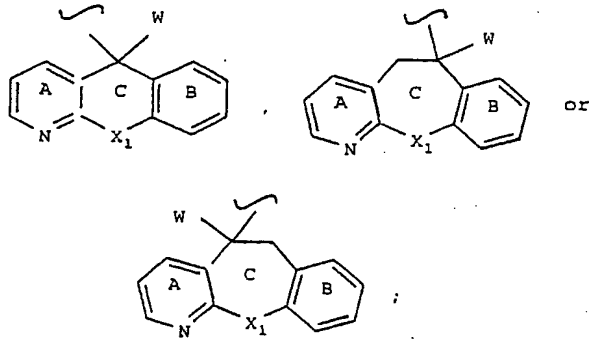


and physiologically acceptable salts thereof, wherein:

L is a $C_1$-$C_{18}$ hydrocarbyl group;

M is >N(alkanoyl), >N(aroyl), >N(aralkoyl), >N(alkyl), >N(aralkyl), >N(cycloalkyl), >C(OH)(aryl) or >CH(heteroaryl);

Z is represented by a structural formula selected from:



wherein:

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$ or $-CO-NR_c-$ ;

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group;

W is -H, -CN, -CH=NH, alkylsulfonyl, carboxamido or carboxyalkyl; and

Ring A, Ring B and Ring C are independently substituted or unsubstituted.

41. The compound of Claim 40 wherein Ring B is substituted with $R^8$ and $R^9$, wherein $R^8$ and $R^9$ are independently -H, a halogen, alkoxy or alkyl, or, taken together with ring B, form a naphthyl group.

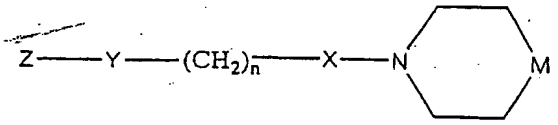
42. The compound of Claim 40 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

43. A compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about five;

X is a covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; and

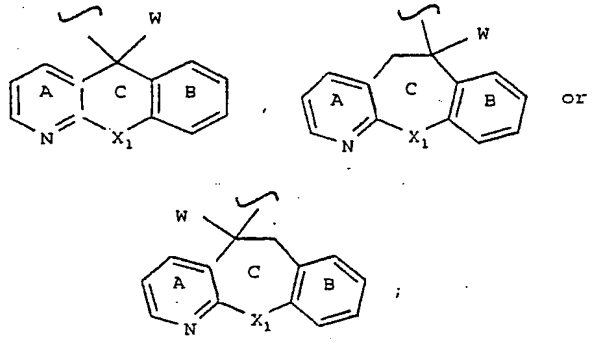
$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic

group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:




;

wherein:

Ring B is substituted or unsubstituted;

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$, $-CO-NR_c-$ ;

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

W is -H or an electron withdrawing group.

44. The compound of Claim 43 wherein Ring B is substituted with -OH, a halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

45. The compound of Claim 43 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

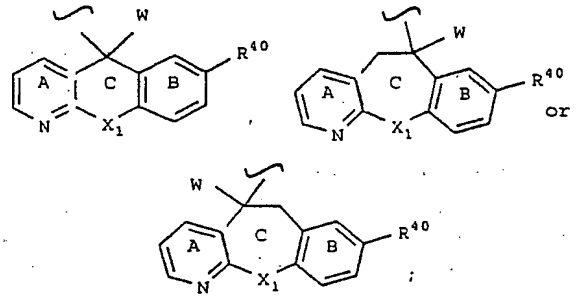
s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

46. The compound of Claim 44 wherein Ring B is substituted para to the carbon atom of Ring B which is bonded to $X_1$

in Ring C, and Z is represented by a structural formula selected from:



wherein $R^{40}$ is -OH, halogen, aliphatic group, substituted aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

47. The compound of Claim 46 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

48. The compound of Claim 46 wherein $R^{40}$ is $-O-CH_3$.

49. The compound of Claim 48 wherein $R^1$ is -OH.

50. The compound of Claim 48 wherein M is $>C(OH)R^2$ and n is three.

51. The compound of Claim 50 wherein:

W is -CN; and

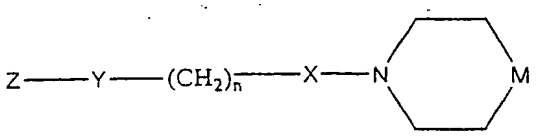
$X_1$ is $-CH_2-O-$, $-CH_2-CH_2-$ or $-CH_2-S-$.

52. The compound of Claim 51 wherein $R^2$ is a substituted or unsubstituted aromatic group.

53. The compound of Claim 52 wherein $R^2$ is an aromatic group that is substituted with a halogen.

54. The compound of Claim 53 wherein $R^2$ is a 4-chlorophenyl group.

55. A compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about five;

X is a single covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; and

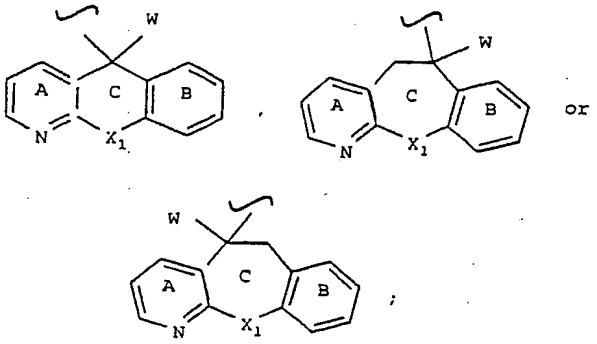
$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic

group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:




wherein:

Ring B is substituted or unsubstituted;

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, -SO-$CH_2$-, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$, $-CO-NR_c-$ ;

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

W is $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

$R^{11}$ and $R^{12}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group;

$R^{11}$ and $R^{12}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

56. The compound of Claim 55 wherein Ring B is substituted with -OH, a halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

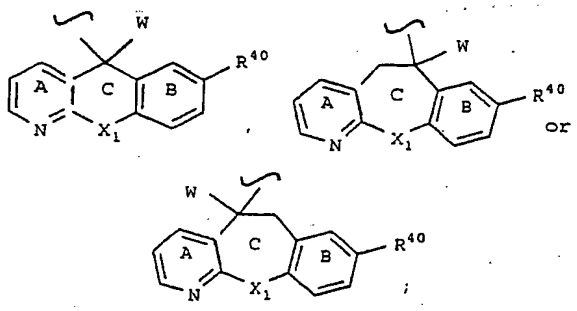
57. The compound of Claim 55 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

58. The compound of Claim 56 wherein Ring B is substituted para to the carbon atom of Ring B which is bonded to $X_1$ in Ring C, and Z is represented by a structural formula selected from:



wherein $R^{40}$ is -OH, halogen, aliphatic group, substituted aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

59. The compound of Claim 58 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

s is an integer from one to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

60. The compound of Claim 58 wherein $R^{40}$ is $-O-CH_3$.

61. The compound of Claim 60 wherein $R^1$ is -OH.

62. The compound of Claim 60 wherein M is $>C(OH)R^2$ and n is three.

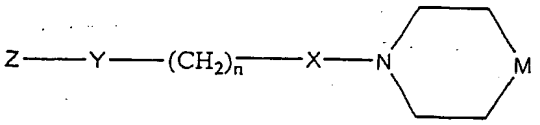
63. The compound of Claim 62 wherein $X_1$ is $-CH_2-O-$, $-CH_2-CH_2-$ or $-CH_2-S-$.

64. The compound of Claim 63 wherein $R^2$ is a substituted or unsubstituted aromatic group.

65. The compound of Claim 64 wherein $R^2$ is an aromatic group substituted with a halogen.

66. The compound of Claim 65 wherein $R^2$ is a 4-chlorophenyl group.

67. A compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about five;

X is a single covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

$R^1$ is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$; and

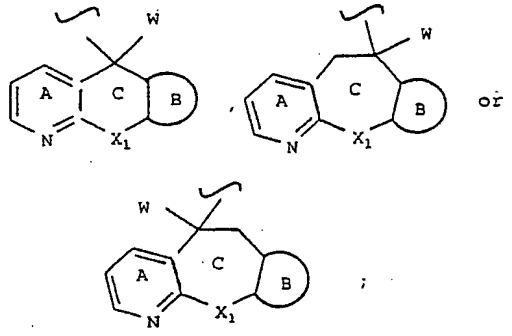
$R^2$ is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl

group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

$R^3$, $R^4$, $R^5$ and $R^6$ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

$R^1$ and $R^2$, $R^3$ and $R^4$, or $R^5$ and $R^6$ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:




wherein:

Ring C is a substituted or unsubstituted non-aromatic carbocyclic ring or a substituted or unsubstituted non-aromatic heterocyclic ring;

Ring B is a substituted or unsubstituted carbocyclic aromatic or heteroaryl group;

$X_1$ is a covalent bond, -S-, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$, $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, -CH=CH-, $-Nr_c-CO-$ or $-CO-NR_c-$ ; wherein:

$R_c$ is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

W is -H, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$, $-CH_2-NHC(O)-O-R^{11}$ or an electron withdrawing group;

$R^{11}$ and $R^{12}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{11}$ and $R^{12}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

68. The compound of Claim 67 wherein Ring B is substituted with -OH, a halogen, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

$R^{20}$, $R^{21}$ or $R^{22}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{21}$ and $R^{22}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

69. The compound of Claim 67 wherein $R_c$ is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from zero to about 3;

$R^{30}$, $R^{31}$ or $R^{32}$ are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

$R^{31}$ and $R^{32}$, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

70. The Compound of Claim 67 wherein $R^1$ is -OH.

71. The compound of Claim 67 wherein M is $>C(OH)R^2$ and n is three.

72. The compound of Claim 71 $R^2$ is a substituted or unsubstituted aromatic group.

73. A method of antagonizing a chemokine receptor in a mammal in need thereof comprising administering a compound of Claim 67.

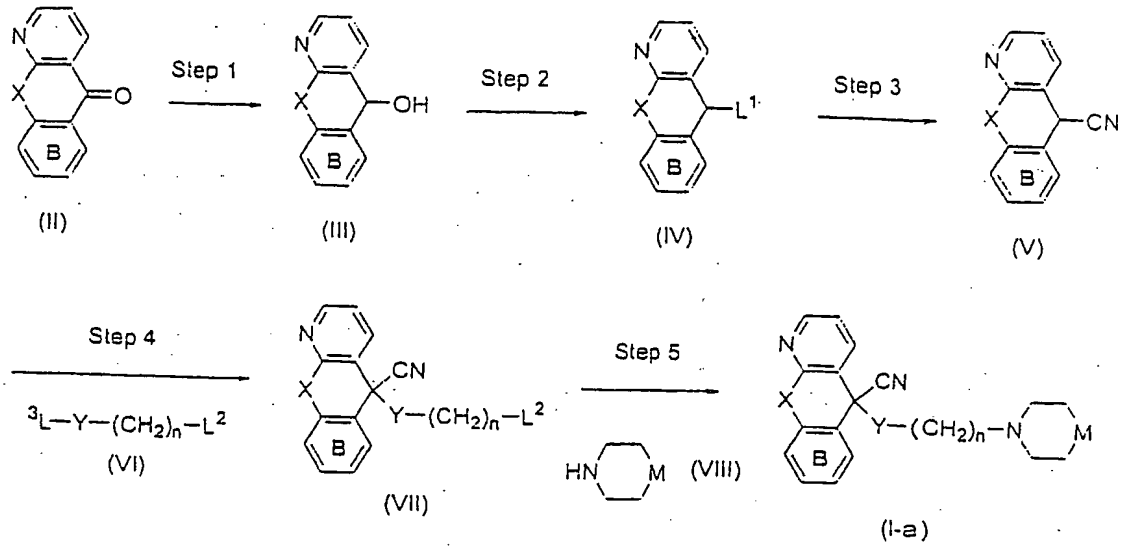
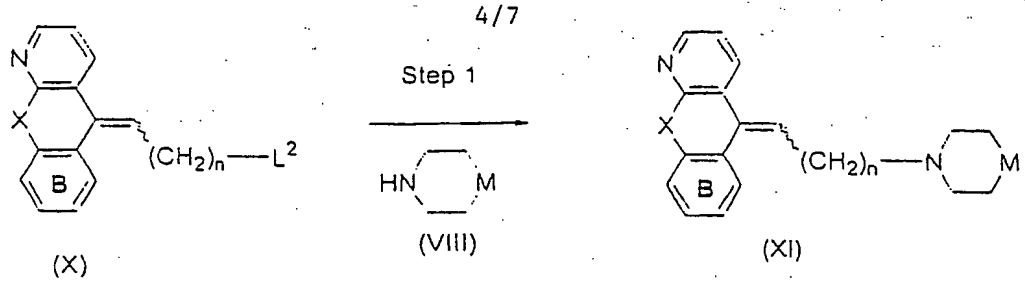



Figure 1



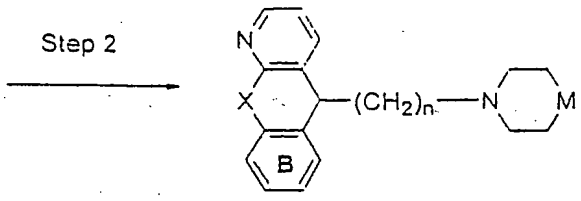




Figure 4

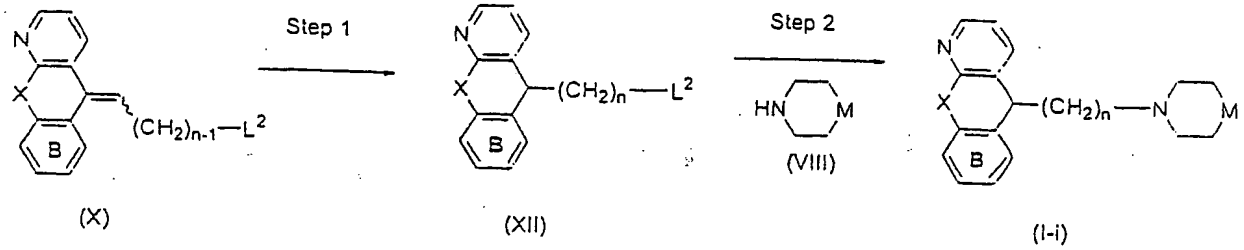



Figure 5

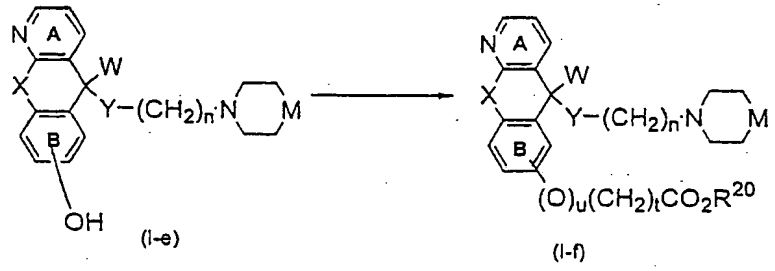



Figure 6

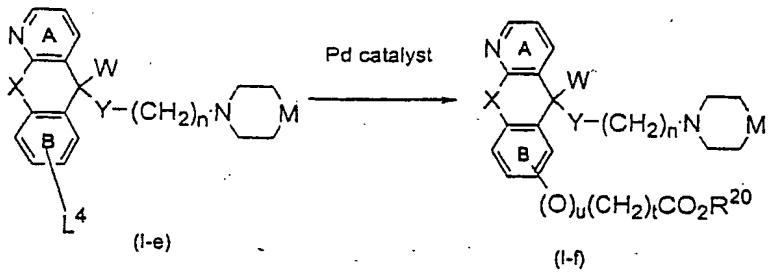



Figure 7

# INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 99/01235

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/044 A61K31/44 A61K31/55 C07D495/04 C07D221/16
C07D471/04 C07D401/06 //(C07D491/044,313:00,221:00),
(C07D495/04,337:00,221:00),(C07D471/04,223:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 98 02151 A (LEUKOSITE) 22 January 1998<br>see claims 1,19 | 1 |
| A | WO 98 04554 A (BANYU) 5 February 1998<br>see abstract<br>-& EP 0 916 668 A (BANYU) 19 May 1999 | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 June 1999 | 16/06/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Alfaro Faus, I |

Form PCT/ISA/210 (second sheet) (July 1992)

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# INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/US 99/01235

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1 to 39 and 73
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1 to 39 and 73 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

rmation on patent family members

Intern al Application No
PCT/US 99/01235

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9802151 A | 22-01-1998 | AU 3659897 A | 09-02-1998 |
| WO 9804554 A | 05-02-1998 | AU 3633997 A | 20-02-1998 |
| | | EP 0916668 A | 19-05-1999 |